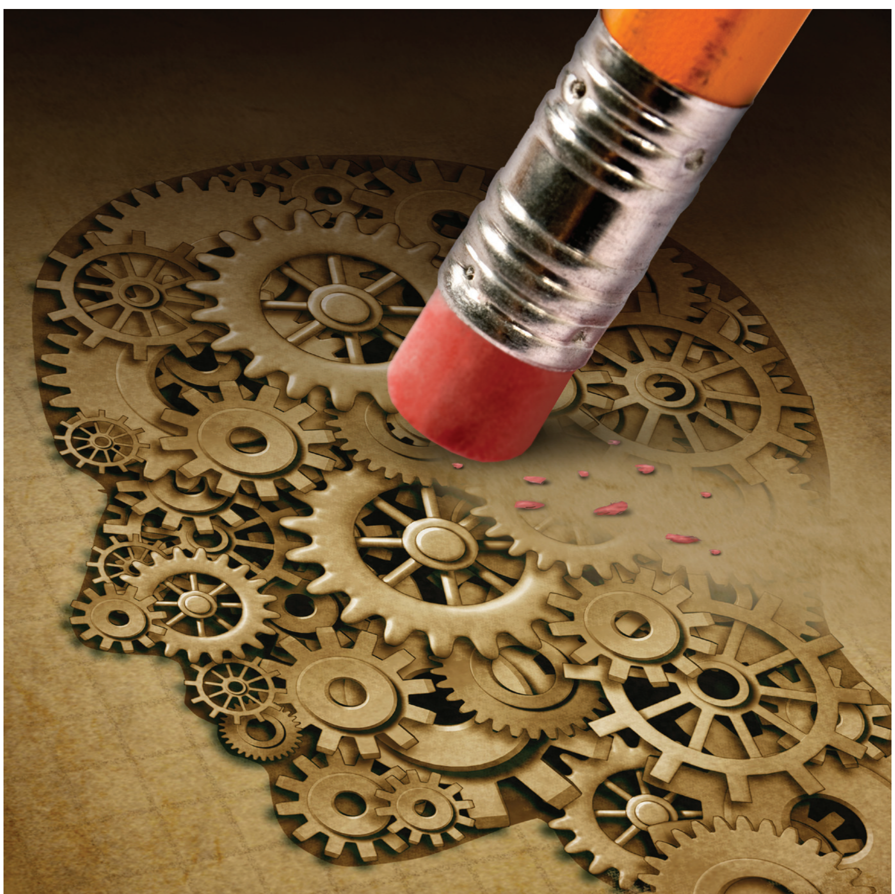
spotlights

Inside Alzheimer's Disease

Los Alamos neutron and x-ray physicist Jarek Majewski is at it again. He has used neutrons to probe biological structures associated with illnesses ranging from cholera to vascular disease [see the August 2011 and August 2014 issues of *1663,* respectively]. To that list, he and his Los Alamos colleague Ann Junghans, together with collaborators at the University of New Mexico, the Max Planck Institute for Neurological Research, and the Center for Neurodegenerative Diseases (the latter two in Germany) now add a mechanism that many researchers believe underlies Alzheimer's disease. The disease is America's sixth-largest killer and burdens the nation to the tune of $220 billion per year—more than 1 percent of GDP—plus another 17 billion hours of unpaid care, according to the U.S. Centers for Disease Control and Prevention and the Alzheimer's Association.

In the brains of patients suffering from Alzheimer's disease—examined post-mortem, of course—anomalous tangles of tau proteins and plaques of beta-amyloid protein fragments are always present. It is not clear whether these tangles and plaques directly cause the disease, but they, or their precursors, are believed to interfere with normal brain function by suppressing communication between neurons or simply disintegrating them. The tau and beta-amyloid proteins are present in healthy human brains as well, where they help stabilize microtubules in the nervous system and participate in cell growth, respectively. But the question is what causes them to accumulate into tangles and plaques in the brains of those suffering from the disease? In other words, what causes these proteins to assemble into larger structures that obstruct the cells' normal activities?

For atoms or molecules to assemble into larger structures like tangles and plaques, they must overcome certain energy barriers; when the aggregates are too small, they are unstable and will disassemble themselves. Sometimes, however, they receive help from tiny bits of solid matter to grow past the unstable phase, such as when clouds are seeded with particles to help raindrops aggregate out of water vapor. Other times, the help comes from environmental conditions, such as fluctuations in temperature, pressure, and electric charge. Something of this sort must be catalyzing the aggregation of beta-amyloid and tau molecules out of solution in Alzheimer's patients, and a theory that has been gaining traction suggests that electrical charges on neuron cell membranes may provide that catalyst.

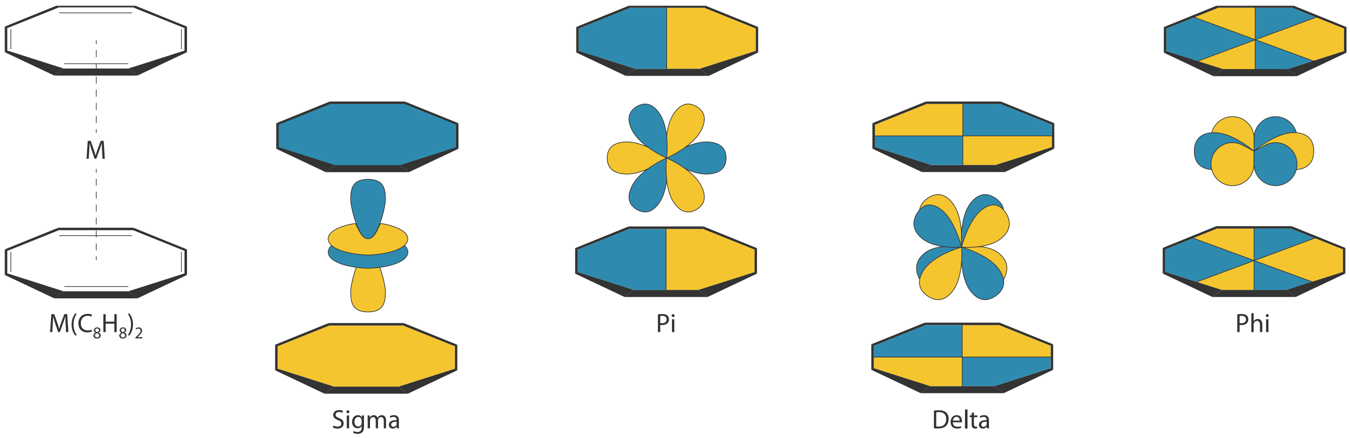


To investigate the theory, Majewski reflected x-rays and neutrons off of a simplified cell membrane after injecting human tau proteins into the adjacent fluid. He found that when the membrane is comprised of uncharged lipids, as is normally the case with the exteriors of young, healthy brain cells, the proteins do not significantly interact with it. But when the membrane contains negatively charged lipids, as are observed in old or injured cells, the tau proteins fold up into tighter configurations—a necessary first step in the aggregation of tau tangles—and wedge themselves between lipid molecules in the cell membrane. Similarly, beta-amyloid proteins anchor into the membrane and begin to aggregate and grow in the presence of the negatively charged lipids. Majewski and his team observed this directly in recent synchrotron x-ray experiments.

In other experimentation using grazing incidence x-ray diffraction and neutron reflectometry, Majewski revealed that the tau proteins broadly disrupt the lipid organization, creating weak spots and openings in the membrane. Such membrane disruptions can impair neuronal signaling and ultimately kill the brain cell—producing (or at least contributing to) the cognitive dysfunction of Alzheimer's patients.

In the absence of the disease, tau proteins bind to microtubules that run the length of the long, wire-like part of neurons, strengthening them and providing convenient roads for other molecules to travel. But if too many phosphate

Los Alamos research indicates that neuron membrane disruption may be responsible for the aberrant growths found in the brains of Alzheimer's patients and the neuronal damage that causes mental decline.



The sandwich complex consists of two flat layers of hydrocarbon atoms which sandwich the metal ion in between. When the metal is thorium, four types of covalent-bond symmetries have now been observed. Each is made by different arrangements of orbitals occupied by electrons involved in the bonding. The yellow and blue shading represent the phase of each orbital lobe, and only orbital lobes of the same phase form constructive interactions—i.e., covalent bonds. Where the metal orbital lobe of one phase (say, blue) is oriented towards a part of the hydrocarbon layer of the same phase (also blue), a bond is formed. The way the hydrocarbon-layer orbitals are split up, like slices of a pie, defines each type of bond—sigma with one slice, pi with two, delta with four, and now phi with six. Note that the pi bond has six visible orbital lobes but only two overlap to participate in bonding with each hydrocarbon layer, as defined by the proximity of matching phases (matching colors) between the thorium in the center and the hydrocarbon layers above and below. The phi bond utilizes the same metal orbital as the pi, but it is rotated in such a way that all six of its lobes overlap with the hydrocarbon-layer orbitals.

groups attach to the tau proteins, as occurs in the early stages of the disease (for unknown reasons), the proteins detach from the microtubules and begin to aggregate into tangles. The process appears to be accelerated by interaction with the interior of the cell membrane where negatively charged lipids are known to reside. Majewski simulated such "hyperphosphorylated" tau proteins in x-ray diffraction experiments with a mutant version of the human tau protein and found that the tau aggregation and lipid membrane disruption were accelerated relative to those for regular tau protein molecules. Then, once the tau aggregates have formed, the continuity of the cell membranes is compromised, killing the cells and making the disease worse over time.

The good news—if learning the mechanisms underlying a horribly debilitating disease can be viewed as good news—is that these studies strongly support the notion that interactions with neuron membranes lead to both neuron death and the formation of protein tangles and plaques. And if both problems have a common cause, they may also respond to a common treatment.

—*Craig Tyler*

Bond, Phi Bond

The principles of chemical bonding lie at the heart of chemistry and have been known since the early 20th century. Therefore, it's not every day that a chemist discovers a new type of chemical bond—but that's exactly what a team led by Los Alamos scientists Stosh Kozimor, Rich Martin, and Enrique Batista, together with Lawrence Berkeley National Laboratory (LBNL) scientist David Shuh, has done.

Prior to this work, covalent bonds (the kind where electrons are shared between atoms) were classified by just three types, named sigma, pi, and delta, which describe the different symmetries of the bonds that hold together molecules at an atomic level. The prize discovery of this work is a fourth type of covalent bond known as the phi bond. Theory had predicted the existence of the phi bond for the actinide metals—the 14 consecutive elements beginning with actinium at the bottom of the periodic table—but experimental proof remained elusive until the Los Alamos and LBNL team developed a way to make the new bond reveal itself. Part of the challenge inherent in studying these elements is the complex organization of their many electrons and the minor role that covalent bonding plays amidst overwhelming ionic forces, which dominate the overall chemical bonding picture. It can be hard to accurately pinpoint these subtle, yet important, covalent-bonding interactions.

The Advanced Light Source (ALS) beamline facility at LBNL allowed the team to take state-of-the-art x-ray absorption spectroscopy measurements on a pair of uranium- and thorium-containing molecules (both actinides). The technique works by examining electronic transitions in which an electron close to the atom's nucleus is excited to a higher-energy state by absorbing an energetic x-ray. When combined with detailed computational models, these transitions can be accurately correlated with a molecule's structure. The compounds—part of a class of molecules called a sandwich complex because the uranium or thorium is sandwiched between two ring-shaped hydrocarbon structures—were carefully chosen because their symmetry simplifies these transitions and allows the team to interpret the x-ray data more clearly.

The plan paid off when the first convincing experimental evidence of the phi bond showed up for the thorium sandwich

complex, as revealed by its elaborate, never-before-seen symmetry. The aptly named sandwich complex normally divides its bonding interactions into specific numbers of segments, like a club sandwich served whole, sliced in half, or sliced in quarters. But the thorium sandwich displayed six slices. No doubt, this new symmetry will be examined in much detail in the future.

Yet the motivation of the work wasn't simply to pin down an elusive form of bonding. It is part of a greater ongoing effort to understand the properties of actinide-containing materials, such as spent nuclear fuel components, in order to improve computer-based models which ultimately may lead to better nuclear separation and forensics technology. But no one can predict all the future benefits of a new scientific discovery, and this one is certainly a landmark for the chemistry of the actinides and the science of chemical bonding in general.

—*Owen Summerscales*

Mathematically Sound Investment

Education research shows that traditional teaching practices, such as covering a chapter a week to get through the textbook by the end of the year, often fall short of the real goal, which is learning. Studies show that it's worth investing time early on to build a solid conceptual foundation before pushing forward to more elaborate tasks.

For example, before children can understand an abstract concept, they must first understand it at the concrete and representational levels. Place three apples in front of a child, and she can pick them up and move them; she can feel and see that there are three distinct units of "apple" in front of her—that's concrete. Now show her a picture of three apples. She can't hold each apple, but she can still see three individual apples—that's representational. Now show her the number "3" without any apples—that's abstract. It seems obvious, but it's not; no matter the grade level, when undertaking a new subject, students benefit from a slow start.

The Los Alamos Math and Science Academy (MSA) sends Laboratory educators into public schools to improve how teachers teach. They train kindergarten through eighth-grade math and science teachers to lead their students through the levels of understanding to real comprehension. In so doing, the MSA supports the Laboratory's good neighbor pledge, which promotes economic development, excellence in education, and active employee engagement in the northern New Mexico community.

Single interventions are ineffective, so rather than a rote hour-long seminar, the MSA provides continual professional development for several years to both teachers and principals. "Educators should engage in professional development from day one, and it should continue throughout their career," says MSA veteran Lorenzo Gonzales. "You are teaching someone to think, you are actually structuring their brain. It's not a simple skill set to be memorized and repeated." With over 40 years of experience, Gonzales is the group's de facto guru. The other three members—Zachary Leonard, Monica Martinez-Archuleta, and Randy Merker—are all former math or science teachers and scholars. They scour the education research literature to identify the latest findings and successful strategies, then translate, hone, and integrate that information into what they call best teaching practices.

Solve the following word problem: Four educators want to teach math to 15,000 grade-schoolers over the course of 14 years. How many students must each educator tutor? Answer: 3,750 total, or 268 per educator per year. That student-teacher ratio, while common at large universities, won't work for elementary school. The formula for the MSA's success is to train the educators so that their investment is amplified with each new class. The program previously partnered with the Taos, Chama, Mora, Española, and Pojoaque school districts in northern New Mexico and is presently working with the Bureau of Indian Education, all with marked success. At the beginning of their work with Native American students in 2005, for example, just 12 percent of students at one school were deemed proficient at math, according to standardized tests. That number has consistently risen through the MSA's partnership and last year reached 56 percent. The numbers add up: the program is working.

And it's not just about how teachers teach, but also what teachers teach. Errors in comprehension are carried over and compounded when teachers don't have a solid understanding of the subject. To address deficits in content knowledge, the MSA brings in Richard Kitchen, a math education professor who spends eight Saturdays per school year teaching math to math teachers at the MSA.

The 2014–2015 academic year is the final year of New Mexico's transition to the Common Core State Standards (CCSS), the national overhaul of public education presently underway, and the members of the MSA have mixed feelings. On the one hand, the CCSS run parallel to the goals of the MSA, and having higher standards ought to result in higher proficiency statewide. On the other hand, they worry that while the bar has been raised, support for teachers statewide may come up short. As Gonzales points out, "High-performance schools have two things in common: opportunities for professional development and the expectation and allowance for teachers to take those opportunities." "While the rest of the state will have to step up to the CCSS, MSA-served schools in northern New Mexico should have a comparatively smooth transition.

—*Eleanor Hutterer*

To most people, a snack; to Los Alamos math-education-theory specialists, a representation of the concept "three."